REMARKS

Claims 1-9 and 25-29 are pending. Claims 10-24 were previously canceled. Claims 7-9 and 27 have been withdrawn by the Examiner as drawn to nonelected species. Applicant respectfully reminds the Examiner that upon finding allowable subject matter, applicant is entitled to have the withdrawn claims rejoined and considered in this application as provided by 37 C.F.R. 1.141. *See* M.P.E.P. § 809.02(a). Claims 1-6, 25, 26, 28, and 29 are under consideration.

Claim 1 has been amended to recite a "therapeutic composition." Support for that amendment is found, for example, at page 44 lines 18-20. Accordingly, no new matter has been added.

Provisional Rejection of Claims 1-6, 25, 26, 28, and 29

The Examiner provisionally rejected claims 1-6, 25, 26, 28, and 29 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-9, 20, 35, 37, 39, 41, and 43 of copending U.S. Application No. 10/744,844. Action at page 2, item no. 4. No action is believed required by the applicant at this time as the alleged conflicting claims have not in fact been patented.

Withdrawal of the Rejection of Claims 1-6, 25, 26, 28, and 29 Under 35 U.S.C. § 112, First Paragraph

Applicant acknowledges, with appreciation, the Examiner's withdrawal of the rejection of claims 1-6, 25, 26, 28, and 29 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Action at page 3, item no. 6.

Rejection of Claims 1-6, 25, 26, 28, and 29 Under 35 U.S.C. § 103(a)

The Examiner maintained the rejection of claims 1-6, 25, 26, 28, and 29 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kumpel et al., Hum. Antibod. Hybridomas 5:143-151 (1994) ("Kumpel") in view of U.S. Patent No. 5,834,251 issued to Maras et al. ("Maras"). Action at page 3, item no. 8.

Applicant respectfully traverses the rejection. Solely to expedite prosecution and without acquiescing to the Examiner's allegations, Applicant has amended the claims to recite a "therapeutic composition." As discussed below, neither Kumpel or Maras, alone or in combination teach or suggest "[a] therapeutic composition comprising a glycoprotein preparation, said glycoprotein having an immunoglobulin CH2 domain said CH2 domain having at least one N-linked oligosaccharide wherein substantially all of the oligosaccharide is a G2 oligosaccharide and wherein the amount of said glycoprotein containing G1 and G0 oligosaccharide does not exceed 10% by weight of the preparation," according to claim 1. The Examiner has failed to establish a *prima facie* case of obviousness.

The Examiner alleges that "Kumpel et al. teach human monoclonal antibodies wherein substantially all of the oligosaccharide found on said antibody is G2 [and that] said antibodies are in composition form wherein they are contained in a pharmaceutically acceptable carrier (e.g. tissue culture media)." Action at page 3, item no. 8. The Examiner acknowledges that "Kumpel et al. do not teach that the antibodies are of the degree of purity recited in the claims or the articles of manufacture of claim 29." Action at pages 3-4.

The Examiner, however, contends that

> Maras et al. teach that B-1,4 Galactosyltransferase can be used to modify the oligosaccharide profile on a glycoprotein (see columns 12 and 16). Kumpel et al. teach that said enzyme is involved in the production of G2 oligosaccharides (see abstract). A routineer would have used the method of Maras et al. to produce a

> more highly purified version of the G2 oligosaccharide containing antibody to further characterize the role of said oligosaccharides in effector function and to produce an antibody with even greater effector function.

Id. at page 4. The Examiner also alleges that

> [i]t would have been prima facie obvious to one of ordinary skill in the art to have created the claimed invention because Kumpel et al. teach that antibodies with substantially all G2 oligosaccharide have increased lysis of target cells in comparison to the same antibody which is produced in a manner that results in low levels of G2 and Maras et al. teach that B-1,4 Galactosyltransferase can be used to modify the oligosaccharide profile on a glycoprotein (eg. to produce highly pure G2 oligosaccharide glycoproteins).

Id.

Applicant respectfully traverses. Applicant previously submitted a response on April 17, 2008, which is hereby incorporated by reference, arguing that the Examiner had not provided a finding of some teaching, suggestion, or motivation to modify the reference or to combine reference teachings to achieve the claimed invention. In response to that argument, the Examiner cited Kumpel at page 146, second column, where it states

> [t]he striking feature of the glycosylation analysis of all three human anti-D MAbs produced in **low cell density** serum-free culture was the remarkably high percentage of oligosaccharide chains bearing two terminal galactose residues (Table 1).

Action at page 5 (emphasis added). The Examiner also referred to Kumpel at page 150, second column, where it states

> [t]hus human monoclonal antibodies produced by EBV-transformed B cells **in hollow fiber culture** may be **more suitable for therapeutic use** than antibodies secreted by hybridomas or heterohybridomas of nonhuman origin because of the **structure of their oligosaccharide moieties**.

Action at page 5 (emphasis added). The Examiner concludes from these passages that "Kumpel et al. . . . teach that antibodies with **substantially all G2 oligosaccharide** have increased lysis of target cells in comparison to the same antibody which is produced in a

manner that results in low levels of G2 and the **potential clinical applications of said antibodies**." *Id.* (emphasis added).

Applicant respectfully disagrees with the Examiner's allegations and conclusions concerning Kumpel. Nevertheless, as stated above, solely to expedite prosecution and without acquiescing to the Examiner's allegations, Applicant has amended the claims to recite a "therapeutic composition." As explained in detail below, Kumpel **teaches away** from using highly galactosylated antibodies in therapeutic applications, and accordingly, teaches away from the claimed therapeutic compositions. Such teaching away is noteworthy because, as provided in the MPEP, "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP § 2141.02(VI). Moreover, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." MPEP § 2143.01(III). "A prior art reference that 'teaches away' from the claimed invention is a significant factor to be considered in determining obviousness. . . ." MPEP § 2145(X)(D)(1).

Kumpel teaches away from the claimed invention as follows. Kumpel explains that **low cell density** serum-free cultures, referred to as **"LD,"** produced MAbs where "the major species (>70%) [is] digalactosyl structures (G2)." Kumpel abstract. Kumpel further explains that MAbs grown in **high density hollow fiber** bioreactors, referred to as **"HD,"** "by contrast, contained about 10% G0 and relatively high levels (over 50%) of monogalactosyl (G1) oligosaccharides." *Id.* Kumpel further discusses that "two **HD MAbs** . . . had glycosylation profiles that were similar to the average value for normal serum serum IgG . . . demonstrating that these human MAbs produced . . . in hollow fiber bioreactors contain 'natural' oligosaccharides which may be

ideal for their therapeutic use." Kumpel indicates that the two HD MAbs, BRAD-3 and BRAD-5, had 29.5% G2 and 35.6% G2, respectively, and that those values were within the range of Serum IgG, which was 20-40% G2. Kumpel at page 141, Table 1, columns 5, 6, and 7. It is these HD MAbs having 20-40% G2 (and 60-80% G0 plus G1) that Kumpel singled out as "ideal for therapeutic use," and not the MAbs grown in low density cultures (LD MAbs) having about 70% G2 (and about 30% G0 plus G1). Thus, Kumpel expressly teaches away from the claimed invention of "[a] therapeutic composition comprising a glycoprotein preparation, said glycoprotein having an immunoglobulin CH2 domain said CH2 domain having at least one N-linked oligosaccharide wherein substantially all of the oligosaccharide is a G2 oligosaccharide and wherein the amount of said glycoprotein containing G1 and G0 oligosaccharide does not exceed 10% by weight of the preparation."

Maras does not cure the deficiencies of Kumpel. Maras is directed to "methods of converting high mannose type glycosylation patters to hybrid or complex type glycosylation patterns" similar to those found on proteins from the higher eukaryotes. See Maras at abstract and col. 2, lines 25-29.

The Examiner alleges that

> Maras et al. teach that B-1,4 Galactosyltransferase can be used to modify the oligosaccharide profile on a glycoprotein (e.g. to produce highly pure G2 oligosaccharide glycoproteins). One of ordinary skill in the art would have been motivated to do the aforementioned in order to produce G2 versions of the aforementioned glycoproteins for potential clinical evaluation.

Action at page 4.

Applicant respectfully traverses. As discussed above, Kumpel expressly teaches away from the claimed therapeutic compositions. Accordingly, one of ordinary skill in the art would

not have been motivated to use β-1,4 Galactosyltransferase as discussed in Maras "to produce G2 versions of the aforementioned glycoproteins for potential clinical evaluation."

In addition, in response to Applicant's previous arguments (Response filed April 17, 2008) concerning the fact that Kumpel discusses the possibility that sialylation differences between antibodies contribute to heterogeneous lysis activity, the Examiner alleges that "a routineer would have not produced antibodies with the negative sialylation profile [and that] the antibodies produced as per Maras et al. would not be sialylated." *Id.* at page 5.

First, Applicant respectfully points out that the less active antibody, JAC10, had 36.8% monosialylated and disialylated glycoprotein as compared to a more active antibody, 2B6, which had 21.7% monosialylated and disialylated glycoprotein. Kumpel at page 145, Table 1, columns 2 and 3. There is simply no teaching or suggestion in Kumpel of G2 oligosaccharide of the present invention which lacks terminal sialic acid. Applicant respectfully points out that he present specification clearly states "G2 refers to a biantenarry structure with two terminal Gals and **no NeuAcs**." Specification at page 11, lines 30-31 (emphasis added). Accordingly, even if "a routineer would have not produced antibodies with the negative sialylation profile," which Applicant does not concede, the "routineer" would not have produced antibodies having the G2 oligosaccharide lacking terminal sialic acid of the present invention.

Second, Applicant respectfully disagrees with the Examiner's interpretation of Maras. Nowhere does Maras teach or suggest antibodies having oligosaccharides lacking sialic acid. In fact, Maras teaches away from antibodies having oligosaccharides lacking sialic acid, consistently emphasizing the desirability of "glycosylation patterns similar to those found on proteins from the higher eukaryotes" and the desirability of sialylation, in particular. *See* Maras at col. 2, line 25 to col. 3, line 17. Each embodiment discussed in Maras describes a protein

having a glycosylation pattern with at least one terminal sialic acid "similar to that of mammalian cells." *See* col. 2, line 31 to col. 3, line 17. Every claim of Maras requires a step of reacting the glycoprotein with sialyltransferase which would result in glycoprotein with at least one terminal sialic acid. Nowhere does Maras teach or suggest "[a] therapeutic composition comprising a glycoprotein preparation, said glycoprotein having an immunoglobulin CH2 domain said CH2 domain having at least one N-linked oligosaccharide wherein substantially all of the oligosaccharide is a G2 oligosaccharide and wherein the amount of said glycoprotein containing G1 and G0 oligosaccharide does not exceed 10% by weight of the preparation," according to present claim 1. Accordingly, for at least the reasons discussed above, one skilled in the art would have had no reason to combine Kumpel with Maras, or to modify either one or both of those documents, as proposed by the Examiner to arrive at the claimed therapeutic compositions.

The Examiner states that "in the post KSR Int'l Co. v. Teleflex Inc. universe, motivation per se in not even required in a rejection under 35 USC 103." Action at page 5. The Supreme Court, however, did not abolish the "teaching-suggestion-motivation" (TSM) test, nor the "motivation" aspect of the test in particular. In fact, the Court expressly stated that "[t]here is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *KSR Intn'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (S. Ct. 2007). As the Court explained, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* Post-KSR decisions of the Court of Appeals for the Federal Circuit have applied this guidance in assessing the validity of claims under § 103, particularly in cases involving the chemical arts. *See, e.g., Takeda Chemical Industries, Ltd. V. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1357

(CAFC 2007) (stating that "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound"). In addition, the MPEP discusses the KSR decision and notes that the Court "recognized that TSM was one of a number of valid rationales that could be used to determine obviousness." MPEP § 2141. Accordingly, the Examiner's position that "motivation per se is not even required" is simply inaccurate, particularly as it applies to the present rejection given that both of the cited documents teach away from the claimed invention.

In summary, there is simply no teaching or suggestion in either of Kumpel or Maras of "[a] therapeutic composition comprising a glycoprotein preparation, said glycoprotein having an immunoglobulin CH2 domain said CH2 domain having at least one N-linked oligosaccharide wherein substantially all of the oligosaccharide is a G2 oligosaccharide and wherein the amount of said glycoprotein containing G1 and G0 oligosaccharide does not exceed 10% by weight of the preparation," according to claim 1. Furthermore, there is simply no motivation to combine Kumpel and Maras or to modify those documents as proposed by the Examiner given that both of the cited documents teach away from the claimed invention. Accordingly, claim 1 would not have been obvious in view of Kumpel and/or Maras. Claims 2-6, 25, 26, 28, and 29 ultimately depend from claim 1 or otherwise include all the elements of claim 1. Therefore, none of the dependent claims would have been obvious in view of Kumpel and/or Maras. Thus, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-6, 25, 26, 28, and 29 under 35 U.S.C. § 103(a) as allegedly being obvious in view Kumpel and/or Maras.

Because the Examiner fails to establish that claims 1-6, 25, 26, 28, and 29 would have been obvious for at least the reasons discussed above, Applicant need not address the Examiner's

contentions concerning other elements of those claims. By not addressing those contentions, applicant in no way acquiesces to those contentions.

CONCLUSION

Applicant respectfully asserts that the claims are in condition for allowance and requests the timely issuance of a Notice of Allowance. Should the Examiner believe that a telephone interview would expedite the prosecution of this application, applicant invites the Examiner to call the undersigned at the telephone number indicated below.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 07-0630.

Respectfully submitted,

GENENTECH, INC.

Dated: September 8, 2008

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